BIBLIOGRAPHY | ABSTRACT | DESCRIPTION | CLAIM | PDF DOWNLOAD

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Priority Claims	95-323710 1995-11-16 Japanese (JP)		
Agent	Koreana Patent Firm	Inventor	ISiKkaWa HiRoMiJji WaTtaNaBe DoMoKko NiSiMuRo SaTtoSi HiRoTta MiSseuRu
Right Holder	JCR Pharmaceuticals Co., Ltd.		
Examiner	Hui-Jin Kim		
Title of Invention	CANCER METASTASIS SUPPRESSOR.		

DRAWING PREVIEW

Click to enlarge the thumbnail below or move the mouse pointer over a figure number to view the drawing in the description.

DRAWINGS

Abstract

The present invention is to provide the novel cancer metastasis suppressor having the low toxicity making the ambulatory treatment possible after operation it is injected through the Cinnabaris to patient in oral in other words it is made of the active ingredient of the ursolic acid or their salt.

Description

- **Details of the Invention**

KR Examined Patent Publication(B1)

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Abstract

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Description

Background Art

The present invention relates to the cancer metastasis suppressor showing the reduced side effect.

One of most big difficulty which is faced in the surgical treatment of tumor are recurrence after operation. It is many. In that case, the metastasis of cancer is the first reason of that recurrence. With forming the lesion which the arm of the second transfers to the separation of the tumor cell of the first lesion, and the breeding at the site falling down of the penetration to the surrounding tissue and body the metastasis of cancer is made of the complicated reaction.

After the tumor cell being separated from the first lesion, it is adjacent and the tridal range interferes with the extracellular matrix consisting of the various collagen existing, the glycoprotein like fibronectin and laminin, and protheoglycan etc to be more diffused. In the meantime, by the tumor cell completely using protease and the various glucosidase secreting with they oneself or the interstitial cell, the extracellular matrix structure is cut and the glucosidase disassemble. It moves.

In this way, the tumor cell separated from the first lesion invades the blood vessel. It is transfered to the boiler falling down. It penetrates into the base film of the blood vessel endothelial cell. Finally it settles in the organization falling down for the breeding.

Consequently, the suppression of the metastasis of cancer is very important as one of the tumor treatment. The platelet aggregation inhibitor, and the various cancer metastasis suppressor like the matrix metalloendoproteinase inhibitor and attach factor inhibitor had been being so far developed as this purpose. Nevertheless, it was not proved that the effective means suppressing the metastasis of cancer was provided.

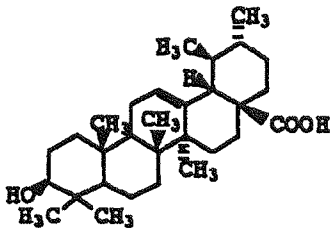
Technical Task

An object of the present invention is to provide the cancer metastasis suppressor which does not have it uses the conventional publicly known chemical treatment drug doing not have any side effect to the active ingredient, and contains the compound showing the metastasis of cancer inhibiting activity of the high efficiency and the increased safety.

Structure & Operation of the Invention

In the point of view of the secure of the improved safety, these inventors noted of the physiologic activity which was evident with the compound which was contained in the plant which could be edible and was naturally generated. In order to find the compound

inducing the inhibiting activity about the metastasis of cancer after the oral administration, research and the huge investigation were performed. It was widely distributed in the apple, and the various kinds of plants like feeling and times to the result. And the ursolic acid indicated by oral and intravenous administration as the following chemical formula 1 suppressing the metastasis of cancer was discovered. It came to the completion of the invention adding the accumulated research after this discovery.



The present invention relates to the cancer metastasis suppressor containing the ursolic acid and their salt to the active ingredient.

The ursolic acid can be the form of the pharmaceutically allowable salt like the free acid or the sodium or the potassium salt.

Preferably the ursolic acid or their salt can be administerd to the adult patient to the daily dose of the range of about 500 mg to oral to paranteral to for example, the means like the injection in other words if the daily dose is hoped.

It is processed to the appropriate mode of administration and it directly can prescribe the ursolic acid or their salt for patient in other words. The concrete example of that mode of administration includes the medication pharmaceutical preparation like the general powder, granule, refinement, capsule and liquid (syrup inclusion). And this pharmaceutical preparation can be according to procedure manufactured. It mixes the additive which is previously used into the ursolic acid. In case of the medication pharmaceutical preparation, the usable additive is the element like excipient (example, and the starch and lactose), binder (example, and the cellulose and polyvinylpyrrolidone), disintegrant (example, and the carboxymethyl cellulose), lubricant (example, and the magnesium stearate), same coating material (example, and the hydroxyethyl cellulose), flavor, coloring agent, preserver and emulsifier or the component which is formerly.

The ursolic acid belongs to the triterpene kind indicated as the chemical formula 1 illustrated as described above. And it has the exceedingly reduced toxicity. And the disadvantageous influence does not reach the breeding of the culture cell to vitro. And it safely can prescribe for patient as if it is confirmed as the fact used as the emulsifier of drug or the food use.

The ursolic acid shows the satisfactory metastasis of cancer inhibiting activity. And this is proved from the experimental example which hereinafter it illustrates. And this has to the melanocarcinoma, fibroid, esophageal cancer, skin cancer, stomach cancer, lung cancer, small intestine and cancer of the colon, the pancreatic cancer, the wool tumor not only the various arm like the breast cancer and bladder cancer, the brain tumor, and the cancer metastasis suppressor about the malignant tumor like the lymph node tumor and leukemia.

The present invention provides the new medicine in which the side effect is reduced of type to patient to oral to the cancer metastasis suppressor having the low toxicity which can be injected to the injection in other words. The medicine contributes to the medicamentous therapy and pharmaceutical industry of tumor.

In order to concretely illustrate present invention, hereinafter, the embodiment is described.

Experimental example 1.

The effect of the ursolic acid about the breeding of the culture cell.

(a) Experimental method.

The human normal fibroblast at the colloidal suspension and B16 F10 melanocarcinoma ($5 \times 10.^4$After the cell) did during being the cell) of canine 2, it did under the presence of the ursolic acid of 0.1 μ M and 1 μ M and member. After cell was put upon another, the number was counted and the effect of the ursolic acid about the cell proliferation was measured.

(b) Experimental result.

In the experimental result shown for the table 1 is the concentration of the , 1 μ M and 0.1 μ M, it shows that any influence the ursolic acid does not reach the breeding of the melanoma cell.

배양 세포에 대한 우르솔릭산의 효과

우르솔릭산의 농도 (M)	증식율 (%)	
	인간 섬유아 세포	악성 흑색종 세포
0.1 μ M	101.3	98.4
1 μ M	99.5	117.7

Main part: it shows in terms of the rate processing the ursolic acid about the number of proliferated cell which the breeding ratio (%) does not process the ursolic acid of the proliferated cell number.

Embodiment 1.

The pharmaceutical preparation for the cancer metastasis restraint manufactures according to below formulation.

Medication formulation.

Ursolic acid 300 mg.

Naphthalene 50 mg.

It becomes with the purified water total 10 ml this.

Injection solution.

Ursolic acid 250 mg.

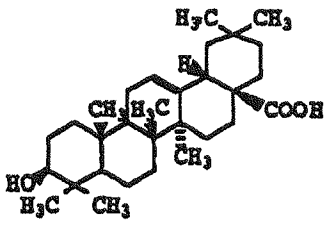
It becomes with the sesame seed oil total 5 ml this.

Embodiment 2.

The experiment about the cancer metastasis restraint of the melanocarcinoma at mouse.

(a) Experimental method.

The colloidal suspension of the B16 F10 malignant melanoma cell was injected into the mouse group consisting of 10 head within vein. The number of lesion administering the oral preparations which contains the ursolic acid during being 13 through 7 to mouse after the injection of the melanoma cell to the once a day oral, and administers the injection solution to the once a day intraperitoneal animal, and takes out the lungs for 14 day, and transfers in each group in the lungs with settlement are irradiated. It was indicated as the following chemical formula 2 having the methyl radical of 29 location which was the ursolic acid and the different location. And the same experiment was performed to the oleanolic acid belonging to the same 5 ring triterpene.



(b) Experimental result.

The experimental result showed in the table 2. The transition showed up according to that within the abdominal cavity after the oral administration to remarkably reduce the transition of the melanoma cell at the lungs in comparision with the control group which did not process ursolic acid.

In the meantime, in the oleanolic acid is the amount of administration of 300 mg/kg, the tridal range, and the suppression noting of the metastasis of cancer are not shown.

우르솔릭산에 의한 암 전이 억제 결과

약품 물질	투여량 (mg/kg)	투여 경로	암 전이 억제율 (%)
대조군	-	-	0
우르솔릭산	100	복강내	66.2 **
우르솔릭산	100	경구적으로	58.7 *
올레아놀산	300	경구적으로	14.5

Main part: significance test.

* P < 0.10 about - control group.

** The p < 0.05 about - control group.

■ Effects of the Invention

The present invention is to provide the cancer metastasis suppressor which does not have any side effect to the active ingredient which does not have in case of the conventional publicly known chemotherapy, and contains the compound having the metastasis of cancer inhibiting activity of the high efficiency and the increased safety.

Scope of Claims

■ Claim 1:

The cancer metastasis suppressor including the ursolic acid or their salt to the active ingredient.

■ Claim 2:

The cancer metastasis suppressor of claim 1, wherein it has the oral administration or scanning as purpose.

■ Claim 3:

The cancer metastasis suppressor of claim 2, wherein 1 daily medication amount in the adult patient is the range of 10 mg - 3,000 mg.

Drawing

Legal Status

Date	Type of Document	Status
19961115	Patent Application	Received
19961115	Submission of Priority Certificate	Received
19970124	Submission of Priority Certificate	Received
20010430	Request for Examination	Received
20010430	Amendment including Specification etc.	Amendment Approved
20030820	Notice of Submission of Opinion	Delivery Completed
20031018	Written Opinion	Received
20040127	Written Decision on Registration	Delivery Completed